## REMARKS

Introductory Comments:

Claims 3, 6-16, 19 and 22-34 were examined in the Office Action under reply. Claims 6, 15, 16, 22, 31 and 32 were indicated as allowable if rewritten to include the recitations from the base claims from which they depend. Claims 3, 7-14, 19 and 23-30 were rejected under 35 U.S.C. §103(a). Claims 3, 6-16, 19 and 22-32 were rejected under the judicially created doctrine of obviousness-type double patenting. These rejections are respectfully traversed as discussed more fully below.

Applicants note with appreciation the withdrawal of the previous rejections under 35 U.S.C. §103(a) as follows: (1) Claims 3, 7, 8, 10-14, 19, 23, 24 and 26-30 over Chien et al., *J. Clin. Microbiol.* (1999) 37:1393-1397 ("Chien-1") in view of U.S. Patent No. 6,306,579 to Seidel et al. ("Seidel") and Choo et al., *Proc. Natl. Acad. Sci. USA* (1991) 88:2451-2455 ("Choo"); (2) Claims 9 and 25 over Chien-1 in view of Seidel and Choo and further in view of Chien et al., *Proc. Natl. Acad. Sci. USA* (1992) 89:10011-10015 ("Chien-2"); and (3) Claims 3, 7-14, 19 and 23-30 over Chien-2 in view of Seidel and Choo. Applicants also acknowledge the withdrawal of the previous obviousness-type double patenting rejections over U.S. Patent Nos. 6,632,601; 6,630,298; 6,428,792 and 6,797,809; as well as over U.S. Application Serial Nos. 10/643,853 and 10/899,715.

Overview of the Above Amendments:

Claims 3 and 19 have been amended to recite that the NS3/4a antigen comprises amino acids 2-686 of SEQ ID NO:2. As explained at page 29, lines 15-17, amino acids 2-686 of SEQ ID NO:2 corresponds to amino acid positions 1027-1711 of HCV-1. Amino acid 1 of SEQ ID NO:2 is an N-terminal methionine. Claims 3 and 19 have also been amended to recite that the consensus sequence from the E2 hypervariable region has the sequence of SEQ ID NO:7. Claim 6 has been amended to track the language of claim 3 from which claim 6 depends.

Support for these amendments can be found in the claims as originally filed and throughout the specification at, e.g., pages 26-27, bridging paragraph; and page 29, lines 14-17.

The foregoing amendments are made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications containing the cancelled and/or unamended claims.

Rejections Over the Art:

The Office maintained the rejection of claims 3, 7, 8, 10-14, 19, 23, 24 and 26-30 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 6,428,792 to Valenzuela et al. ("Valenzuela") in view of U.S. Patent No. 6,306,579 to Seidel et al. ("Seidel") and Choo et al., *Proc. Natl. Acad. Sci. USA* (1991) 88:2451-2455 ("Choo"). The Office argues Valenzuela teaches MEFA-3, MEFA-5 and MEFA-6 that include "epitopes from the NS3/NS4a(helicase) region." Office Action, page 5. Seidel is cited for teaching a double antigen bridge test and Choo is said to teach a sequence 99.5% identical to SEQ ID NO:2. However, applicants respectfully submit that this combination fails to render the present invention obvious.

To support an obviousness rejection under 35 U.S.C. §103, "all the claim limitations must be taught or suggested by the prior art." MPEP §2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." MPEP §706.02; *In re Vaeck,* 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants submit that the cited references do not disclose or suggest all the limitations of the present invention. Thus, a *prima facie* case of obviousness has not been presented by the Office.

In particular, as explained to the Office in the previous Amendment, Valenzuela fails to describe a double antigen bridge assay method and does not describe the use of a conformational epitope of NS3/4a. Similarly, Seidel completely fails to teach or suggest the use of any MEFA, and certainly not the particular MEFAs used in the claimed assays. Seidel also fails to teach the use of **both** a MEFA and an NS3/4a antigen in an assay. As with Seidel, Choo does not describe an assay as claimed, using both a MEFA and an NS3/4a antigen including a conformational epitope. The polyprotein described in Choo includes over 3000 amino acids and there is no suggestion or teaching as to the boundaries of particular HCV regions of the polyprotein, such as the NS3/4a region, now known to be present in the polyprotein. Moreover, Choo on its face

states that the identities of the various regions had not yet been determined. Therefore, Choo fails to provide any guidance with respect to the use of an NS3/4a epitope and provides no suggestion or motivation to use this particular unidentified epitope in assays with an NS3/4a antigen as claimed.

The Office disputes these arguments and asserts Valenzuela teaches the use of MEFAs with NS3/NS4a epitopes for binding HCV-specific antibodies; that Seidel teaches a format for using HCV antigens from NS3 and that Choo has an internal sequence that is 99.5% identical to SEQ ID NO:2. However, none of the cited art provides a suggestion to use the particular NS3/4a sequence presented in the amended claims, namely, SEQ ID NO:2. As explained at page 29, lines 14-20, the sequence of SEQ ID NO:2 differs from the native sequence found at amino acids 1027-1711 of HCV-1.

MEFA-3 of Valenzuela includes amino acids 1192-1457 of the NS3 region and amino acids 1694-1735 of the NS4 region. MEFA-5 and MEFA-6 of Valenzuela include amino acids 1192-1457 of the NS3 region and amino acids 1689-1735 of the NS4 region. It is readily apparent that the NS3/NS4 epitopes used in Valenzuela do not include amino acids 1027-1191 and are therefore missing a large region present in applicants' NS3/4a antigen. Moreover, there is no suggestion in Valenzuela to use the particular sequence specified in SEQ ID NO:2. Similarly, Seidel's NS3 antigen includes amino acids 1207-1488 and therefore lacks major portions of applicants' NS3/4a antigen. With respect to Choo, this reference provides the entire HCV polyprotein sequence and does not delineate the NS3/4a region, let alone the particular NS3/4a antigen used by applicants which is different than the native sequence provided in Choo.

It appears that the Office is in agreement, as claims 6 and 22, pertaining to the use of SEQ ID NO:2 *per se*, were not included in this rejection. As seen above, the claims have been amended to eliminate the recitation of percent identity. None of the cited art, either alone or in combination, teaches or suggests the use of the particular NS3/4a antigen used by applicants. Accordingly, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

The rejection of claims 9 and 25 over Valenzuela in view of Seidel and Choo, and further in view of Chien et al., *Proc. Natl. Acad. Sci. USA* (1992) 89:10011-10015 ("Chien-2"), was also maintained. The combination of Valenzuela, Seidel and Choo is applied as described above.

Chien-2 is said to teach "that the c33c polypeptide appears to encode both a viral protease and helicase." Office Action, page 7. However, applicants do not agree that this combination renders the claims obvious.

Applicants have explained above why the combination of Valenzuela in view of Seidel and Choo is not applicable to the base claims from which claims 9 and 25 depend. Chien-2 does not cure the deficiencies of Valenzuela, Seidel and Choo. Namely, Chien-2 does not provide or suggest the particular NS3/4a sequence present in the claims. As explained on page 10011, at line 8 of the Materials and Methods section, the C33C antigen used in Chien's C25 chimeric antigen included only 266 amino acids. The full-length helicase domain spanning amino acids 1193-1657 as claimed in claims 9 and 25, on the other hand, includes 465 amino acids, and is therefore almost 200 amino acids longer! The Office, however, reasons Chien-2 suggests the use of helicase epitopes and that the "shorter helicase as recited on page 10011 at line 8 is sufficient" in order to sustain the rejection. Office Action, page 7. However, there is absolutely no indication in Chien-2 regarding just which 266 amino acids of NS3 were used and no teaching or suggestion in Chien-2 of a MEFA containing the full-length helicase region of NS3, spanning amino acids 1193-1657, and the use of such a MEFA in assays as claimed. There is no disclosure in Chien-2 or any of the other art cited in the combination regarding the particular NS3/4a antigen recited in the claims.

Thus, as with the combination above, the present combination fails to teach or suggest all of the claim limitations. Accordingly, withdrawal of the rejection of claims 9 and 25 over Valenzuela in view of Seidel and Choo, and further in view of Chien-2 is respectfully requested.

Claims 3, 7, 8, 10-14, 19, 23, 24, 26 and 30 stand newly rejected under 35 U.S.C. §103(a) as being unpatentable over Chien et al., *J. Clin. Microbiol.* (1999) 37:1393-1397 ("Chien-1"), Seidel and Choo, in view of Wang et al., *Chinese J. Exp. Clin. Virol.* (2000) 14:141-144 ("Wang"). Claims 3, 7-14, 19 and 23-30 were newly rejected under 35 U.S.C. §103(a) as unpatentable over Chien-2, Seidel and Choo in view of Wang. Similarly, claims 9 and 25 were rejected under 35 U.S.C. §103(a) as unpatentable over Chien-1 in view of Seidel and Choo, and further in view of Chien-2 and Wang.

In each of these combinations, the Examiner correctly recognizes that Chien-1, Chien-2, Seidel and Choo "do not teach the use of an E2 hypervariable consensus sequence spanning

amino acids 390-410." Office Action, pages 10, 11 and 12. Wang is cited for purportedly teaching "the use of multiple antigen peptide corresponding to the HCV hypervariable region 1 consensus sequence within E2/NS1 spanning amino acids 390-411." Office Action, pages 10, 11 and 12. However, a review of Wang shows that the consensus sequence presented therein is not the same as applicants' consensus sequence presented in SEQ ID NO:7. See, the "Most Common" sequence shown in Figure 1 of Wang. All of applicants' claims specify that the consensus sequence is the sequence of SEQ ID NO:7. This sequence is not taught or suggested by any of the cited references. Additionally, as explained above, the particular NS3/4a antigen used in the claimed methods also is not taught or suggested by the cited combinations. Thus, an obviousness rejection over the combinations of Chien-1 and/or Chien-2 with Seidel, Choo and Wang, simply cannot be sustained. Withdrawal of these bases for rejection is respectfully requested.

Applicants submit that all of the stated combinations fail to provide a proper basis for an obviousness rejection. In the absence of some teaching or suggestion in the cited references concerning the particular NS3/4a antigen and E2 hypervariable region used in the claimed methods, the Examiner has presented no more than an improper hindsight reconstruction of the present invention.

It is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (emphasis added):

> While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Virtually all inventions are combinations of elements that can be individually identified in multiple references. See, e.g., *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998), noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in the references but, rather, whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458. In the pending case, the Office has not met this burden.

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP 2143). It is respectfully submitted that the Examiner has not provided such knowledge. Instead, the Examiner has merely asserted that it would have been obvious to combine various components to arrive at applicants' claimed method. However, none of the cited references specifically teach or suggest methods using applicants' particular NS3/4a antigen and E2 hypervariable region consensus sequence.

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

As also stated by the Court of Appeals for the Federal Circuit "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

The Obviousness-type Double Patenting Rejections:

The Office has maintained the provisional rejection of claims 3, 6-16, 19 and 22-32 over claims 1-49 of copending U.S. Application No. 10/174,652 under the judicially created doctrine of obviousness-type double patenting. Applicants note the Office has agreed to hold this rejection in abeyance until allowable subject matter is indicated in either or both of the instant application and/or the '652 application. Applicants will then consider the propriety of filing a terminal disclaimer vis-a-vis the allowed claims.

## CONCLUSION

Applicants respectfully submit that the claims define a patentable invention. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

Marcella Lillis
Novartis Vaccines & Diagnostics
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-8406
Facsimile: (510) 655-3542.

Respectfully submitted,

Date: 4/27/06

By: _____

Roberta L. Robins
Registration No. 33,208
Attorney for Applicants

NOVARTIS VACCINES & DIAGNOSTICS
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097